22-1258, 22-1307

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV,

Plaintiffs-Appellees,

—v.—

TEVA PHARMACEUTICALS USA, INC., MYLAN LABORATORIES LIMITED,

Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
JUDGE CLAIRE C. CECCHI
2:18-CV-00734-CCC-LDW, 2:19-CV-16484-CCC-LDW

BRIEF FOR PLAINTIFFS-APPELLEES [NON-CONFIDENTIAL]

BARBARA L. MULLIN
ARON FISCHER
ANDREW D. COHEN
MEGHAN R. LARYWON
A. ROBERT QUIRK
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, New York 10036
(212) 336-2000
bmullin@pbwt.com
afischer@pbwt.com
acohen@pbwt.com
mlarywon@pbwt.com
rquirk@pbwt.com

Attorneys for Plaintiffs-Appellees

U.S. PATENT NO. 9,439,906 CLAIMS 1, 2, 8, 10, 11, 13, 19, 20, AND 21 (APPX174-175)

1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

2. The dosing regimen of claim 1 wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals.

8. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 75

mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

10. The dosing regimen of claim 8 wherein the sustained release formulation is an aqueous nanoparticle suspension.

11. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for psychotic disorder comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.

13. The dosing regimen of claim 11 wherein the psychiatric patient is in need of treatment for of a psychotic disorder wherein the psychotic disorder is schizophrenia.

19. The dosing regimen of claims 1, 4, 8 or 11 wherein the sustained release depot formulation is an aqueous nanoparticle suspension consists essentially of

(a) 156 mg/ml of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm;

(b) 12 mg/ml of polysorbate 20;

(c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5);

(d) 30 mg/ml of a suspending agent wherein the suspending agent is polyethylene glycol 4000; and

(f) water q.s. ad 100%.

20. The dosage regimen of claim 19 wherein in the buffering agents contained in the aqueous nanoparticle suspension are citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide.

21. The dosage regimen of claim 19 wherein in the pH of the aqueous nanoparticle suspension is in the range of pH 7 to 7.5.

CERTIFICATE OF INTEREST

Counsel for Plaintiffs-appellees Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica, NV certifies the following:

1. **The full name of all entities represented by us are:**

   Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica, NV.

2. **The names of the real parties in interest:** N/A.

3. **Parent corporations and publicly held companies that own 10% or more of the stock in the parties represented by us:**

   Johnson & Johnson. No other publicly held corporations owns 10% or more of the stock in Johnson & Johnson.

4. **The names of all law firms, partners, and associates who appeared for the parties now represented by us in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:**

   PATTERSON BELKNAP WEBB & TYLER: Zhiqiang Liu, Joong Youn (Jay) Cho, Jeffrey Hughes, Margaret O'Neil

   ROBINSON MILLER LLC: Keith J. Miller, Michael J Gesualdo.

   AKIN GUMP STRAUSS HAUER & FELD LLP: Angela Verrecchio, Matthew A. Pearson.

5. **The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect of be directly affected by this court's decision in the pending appeal:**

   Janssen Pharmaceuticals, Inc. v. Pharmascience Inc., 2-19-cv-21590 (D.N.J.); *Janssen Pharmaceuticals, Inc. v. Tolmar, Inc.*, 1:21-cv-1784 (D. Del.); and *Janssen Pharmaceuticals, Inc. v. Accord Healthcare Inc.*, 2:22-cv-856 (D.N.J.).

6. Any information required under Fed. R. App. P. 26.1(b) and (c), which identify organizational victims in criminal cases and debtors and trustees in bankruptcy cases: N/A.

TABLE OF CONTENTS

TABLE OF CONTENTS
(continued)

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF CONTENTS
(continued)

Page

CONFIDENTIAL MATERIAL OMITTED

The material redacted in the non-confidential version of this brief, and marked in the confidential version, at page 67, concerns specific measurements of Teva products, the details of which Teva designated confidential under the terms of the protective order in D.N.J. Case No. 18-cv-734.

To Appellees' knowledge, the foregoing material was treated as confidential during the district court proceedings and not revealed in publicly available filings or in proceedings open to the public.

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF AUTHORITIES
(continued)

Page(s)

TABLE OF AUTHORITIES
(continued)

Page(s)

TABLE OF AUTHORITIES
(continued)

Page(s)

STATEMENT OF RELATED CASES

No appeal in or from the same civil action or proceeding in the tribunal below was previously before this Court or any other appellate court.

Appellees are asserting the patent at issue in this case, U.S. Patent No. 9,439,906, against other parties in the following pending cases: *Janssen Pharmaceuticals, Inc. v. Pharmascience Inc.*, 2:19-cv-21590 (D.N.J.); *Janssen Pharmaceuticals, Inc. v. Tolmar, Inc.*, 1:21-cv-1784 (D. Del.); and *Janssen Pharmaceuticals, Inc. v. Accord Healthcare Inc.*, 2:22-cv-856 (D.N.J.). Those cases may directly affect or be directly affected by this Court's decision in this appeal.

INTRODUCTION

After a twelve-day trial, the district court concluded that Appellant Teva Pharmaceuticals USA Inc. ("Teva") failed to prove by clear and convincing evidence that the asserted claims of U.S. Patent No. 9,439,906 (the "'906 patent") were invalid. The district court's conclusion was correct. The claims of the '906 patent describe unique dosing regimens for the long-acting injectable ("LAI") antipsychotic paliperidone palmitate, the commercial embodiment of which is Invega Sustenna®. As the district court found, the claimed dosing regimens embody a novel approach to dosing LAIs that went against the conventional wisdom, helped address the vexing problem of patient adherence to medication, and led directly to the spectacular commercial success of Invega Sustenna. Teva's evidence, which hinged on the testimony of an obviousness expert with "credibility issues," Appx72-73 n.25, fell far short of proving that the claimed inventions would have been obvious or that certain claims were indefinite. Appellants fail to establish error in the district court's decision.

First, the district court did not require Teva to prove obviousness of unclaimed elements of the asserted claims. Rather, the district court concluded that Teva failed to prove that a person of ordinary skill in the art ("POSA") would have been motivated to modify the prior art to arrive at the claimed inventions with a reasonable expectation of success. When the court found that a desire to safely

achieve rapid efficacy would not have motivated a POSA to arrive at what Teva termed the "general dosing regimens" of claims 2 and 20-21, Appx10327-10328(327:25-328:4), it was simply rejecting the theory of motivation offered by Teva's expert. *See, e.g.*, *Immunex Corp. v. Sandoz, Inc*., 964 F.3d 1049, 1066-67 (Fed. Cir. 2020); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1368 (Fed. Cir. 2016). And when the court found that a POSA would not have had a reasonable expectation of success based in part on the lack of prior-art clinical studies of the schizophrenia patient population, it was correctly relying on trial evidence to find as a matter of fact that a POSA would have considered the absence of clinical data important. *See, e.g.*, *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1346-47 (Fed. Cir. 2021).

Second, the district court did not "overemphasi[ze] . . . the importance of published articles and the explicit content of issued patents," *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 419 (2007), nor did it disregard the "[p]erspective of a [s]killed [a]rtisan," Appellants' Br. ("Br.") 48. Precisely the contrary. The district court relied extensively on the testimony of skilled scientists from both parties to determine what teachings a POSA would have drawn from the prior art. It was not error, much less clear error, for the district court to find Janssen's expert witnesses

more credible than Teva's, and to reject the attorney-driven perspective on the art that Appellants advocate on appeal.

Third, the district court did not err in deciding that Teva failed to prove the indefiniteness of the claims reciting a specific particle-size range for the claimed formulation. The district court correctly recognized that different measurement techniques render a claim indefinite only when there is evidence that the "different measurement techniques in fact produce[] significantly different results." *Takeda Pharm. Co., Ltd. v. Zydus Pharms. USA, Inc*., 743 F.3d 1359, 1367 (Fed. Cir. 2014). The court then correctly found that Teva had failed to establish these facts.

COUNTER-STATEMENT OF THE QUESTIONS PRESENTED

1. Did the district court correctly conclude, based on factual findings that were not clearly erroneous, that Teva failed to prove the asserted claims would have been obvious?

    a. Did the district court correctly apply the law of obviousness, without improperly adding limitations to the claims, when it rejected the opinions of Teva's expert witness that a motivation to "reach therapeutic plasma levels faster," Appx1426, would have led a POSA to claims 2 and 20-21, which Teva described as "general" dosing

regimens intended for the "general population"? Appx10325-10326(325:18-326:3); Appx10327-10328(327:22-328:4).

b. Was the district court correct, and not clearly erroneous, to find that a POSA would have lacked a reasonable expectation of success in treating a patient with the dosing regimens of claims 2 and 20-21, based, in part, on the absence of prior-art clinical data suggesting that these dosing regimens would be safe and effective in a population of schizophrenic patients?

c. Did the district court properly consider the evidence from the perspective of a POSA, and make findings that were correct, and not clearly erroneous, when it accepted the testimony of Janssen's expert as "credibl[e]," Appx72; Appx85, and rejected the testimony of Teva's expert as based on "impermissible hindsight" and marred by "credibility issues"? Appx72-73 n.25.

d. Did the district court correctly conclude, without improperly adding limitations to the claims, that claims 10 and 13 would not have been obvious, rejecting Teva's argument that a POSA, motivated to create a dosing regimen for patients with mild renal impairment, would reduce by 50% the regimen claimed for the general population? Appx10333(333:6-12).

e. Were the district court's detailed fact-findings regarding the many objective indicia that supported a finding of nonobviousness correct, not clearly erroneous, and relevant to its ultimate conclusion of nonobviousness?

2. Was the district court correct, and not clearly erroneous, in concluding that Teva failed to prove the indefiniteness of claims 20-21 (reciting a specific particle-size range), when it found that Teva failed to prove that different measuring techniques gave meaningfully different results for particle size?

COUNTER-STATEMENT OF THE CASE

A. Treatment of Schizophrenia Prior to the Claimed Inventions

Schizophrenia is a debilitating illness for which there is no cure. Appx11875-11878(1875:19-1878:16); Appx10083-10084(83:2-84:21). The symptoms of schizophrenia can be treated with antipsychotic medications. Appx10084(84:22-24); Appx11886-11887(1886:11-1887:10). But if the symptoms are not properly treated, the "brain pays a price," with successive psychotic episodes leading to progressive and permanent damage. Appx11885-11886(1885:21-1886:13); Appx11887-11888(1887:14-1889:20). Early and consistent treatment soon after onset of the disease is therefore critical to achieving remission and improving a patient's prognosis. Appx11884-11886(1884:4-1886:13); Appx11878(1878:8-16).

One of the most significant challenges in the effective treatment of schizophrenia is adherence, since the symptoms of the disease often render patients unwilling or unable to take their oral medication regularly. Appx11887-11889(1887:16-1889:20). When patients stop taking their oral medication, symptoms rapidly recur, resulting in a cycle of non-adherence and further relapses. *Id.*

LAI antipsychotics address these adherence challenges. Appx11889-11890(1889:21-1890:7). Because they are dosed less frequently than oral medication and are administered by healthcare professionals, LAIs can make it easier for patients to take their medication regularly and for doctors to monitor adherence. Appx10085-10086(85:17-86:4); Appx10090-10091(90:24-91:15); Appx11889-11890(1889:21-1890:7). As of December 2007, however—the time of the invention[1]—the available LAI antipsychotics had significant shortcomings that limited their ability to improve patient outcomes.

First, because high doses of LAI antipsychotics carry the risk of severe and extended side effects, the prevailing wisdom counseled in favor of "starting low and going slow"—*i.e.*, starting with a low dose and gradually adjusting the dose upwards, typically supplementing with oral medication to ensure effective treatment in the meantime. Appx95; Appx11899-11901(1899:11-1902:7);

[1] Appellants do not contest this priority date on appeal. Br. 19.

Appx11932(1932:2-11); Appx56120. But this approach meant that, for a significant time at the beginning of LAI treatment, patients needed to take oral medication to control their symptoms. Appx11082(1082:3-19); Appx11899-11900(1899:11-1900:21); Appx11904-11906(1904:20-1906:10). This led to the same adherence challenges LAIs were intended to solve.

Second, all but one of the LAIs available at the time of the invention were so-called "first-generation" (or "typical") antipsychotics. Appx11906(1906:4-7); Appx12388(2388:2-7); Appx12409(2409:10-19). These drugs are associated with severe side-effects. Appx57-58; Appx11891-11895(1891:11-1895:22); Appx12393(2393:2-21); Appx12399(2399:13-24). By 2007, "second-generation" or "atypical" antipsychotics, which have less severe (though still significant) side effects, were the standard of care for most schizophrenia patients. Appx11903-11904(1903:17-1904:19); Appx56074-56078; Appx56120. First-generation LAIs were generally restricted to chronically ill patients in institutionalized settings with little hope of achieving remission. Appx11897-11898(1897:5-1898:18); Appx11917-11918(1917:20-1918:7).

Finally, the one second-generation LAI available in the United States as of December 2007, Risperdal Consta® (risperidone), had several limitations related to its dosing regimen. Appx58; Appx11904-11906(1904:17-1906:10). Risperdal Consta was dosed according to the "start low, go slow" paradigm,

required oral supplementation for three weeks after the first injection, and had a "narrow" two-week dosing interval. Appx11904(1904:17-1905:19); Appx11918(1918:8-18); Appx17941; Appx10168-10169(168:19-169:5). This dosing regimen limited Risperdal Consta's ability to meaningfully improve patient adherence. Appx11904-11905(1904:17-1905:19).

B. The Invention of the Claimed Dosing Regimens

Recognizing the need to improve upon Risperdal Consta, Janssen set out to develop a second-generation paliperidone palmitate LAI that could deliver rapid and sustained efficacy without oral supplementation. Appx10751(751:1-20); Appx10753-10754(753:9-754:2); Appx20677. As the district court found, the development of Invega Sustenna took over a decade, with numerous setbacks along the way, before the inventors ultimately succeeded in inventing a novel formulation and dosing regimen that turned the conventional "start low and go slow" dosing paradigm on its head and led Invega Sustenna to become the most widely used second-generation LAI in the U.S. by a large margin. Appx58-62; Appx95.

1. Perfecting the Formulation

From the mid-1990s until the mid-2000s, Janssen worked to perfect the formulation for a paliperidone palmitate LAI. Appx58-59; Appx10759-10760(759:15-760:9); Appx10761-10762(761:11-762:15); Appx10772-

10773(772:20-773:10); Appx10782-10783(782:24-783:19); Appx48256. In 1998, Janssen scientists filed the application that became U.S. Patent No. 6,555,544 (the "'544 patent"), reflecting early work on the LAI paliperidone palmitate formulation. Appx13237. But in 1999, results of a Phase I study revealed that the then-leading formulation candidate released paliperidone palmitate too slowly. Appx10760-10762(760:11-762:15). Dr. Alfons Wouters, an inventor of the '906 patent, improved the formulation by altering the particle size of paliperidone palmitate, which he hypothesized was driving the release profile. Appx10761-10763(761:22-763:8). Dr. Wouters developed numerous iterations of the formulation until perfecting the Invega Sustenna formulation (F13) in 2005. Appx10782-10783(782:24-783:19); Appx48256. F13 meets the elements of claims 20 and 21. Appx11611-11614(1611:25-1614:19); Appx54684. Although Teva points out that the ***composition*** of F13 was disclosed in International Patent Publication No. WO2006/114384 ("WO 384") (Br. 14), neither WO 384 nor any prior art reference discloses the ***particle size*** range of F13, Appx11544-11545(1544:24-1545:1), which helps ensure sustained efficacy.

2. The Failed Phase III Trials

In 2004-2005, Janssen initiated three Phase III clinical trials of LAI paliperidone palmitate—PSY-3002, PSY-3003, and PSY-3004. Appx60; Appx10778-10779(778:19-779:22); Appx11054-11055(1054:2-1055:3). The trials

cost tens of millions of dollars, reflecting Janssen's significant commitment to this technology. Appx11034(1034:15-25); Appx11108(1108:3-10). The summary of the protocol of the PSY-3003 trial, without any study results, is NCT00210548 (the "548 Protocol"), Appx13244, one of Teva's primary prior art references, Appx68-69 & n.18. These placebo-controlled Phase III trials employed similar dosing regimens. Collectively, they studied the administration of ***equal*** doses of either 25, 50, 100, or 150 mg-eq. of paliperidone palmitate into the ***gluteal*** muscle on days 1, 8, 36, and 64 of treatment. Appx11050-11051(1050:4-1051:23); Appx33982-33986; Appx36398-363401.

As the district court found, all three trials were "failures." Appx60. The results from PSY-3004 were a "disaster." Appx11055-11056(1055:4-1056:18). None of the doses studied in PSY-3004 were effective in United States subjects and, even in the international study population, the dosing regimens did not achieve rapid efficacy, with separation from placebo not observed until day 36 of treatment. *Id.*; Appx11060-11061(1060:7-1061:11); Appx22782-22785. The PSY-3003 results were "even worse." Appx11061(1061:12-24). Again, there was no efficacy for U.S. subjects, no dose was effective for any subjects before day 36, and only one of the three tested doses showed any efficacy at all. Appx22786-22792.

Based on these results, Janssen estimated only a 16% chance of FDA approval, Appx11068(1068:3-11); Appx22815, and assessed that the tested dosing regimens would "not lead to the efficacy that this product needs to have in the market place," Appx56123. Inventor Dr. Srihari Gopal thought the project might be terminated and he might be fired. Appx11056-11057(1056:19-1057:9). Inventor Dr. An Vermeulen described the failure of the Phase III trials as a "crisis moment." Appx10784-10785(784:1-785:18).

3. Conception of the Claimed Dosing Regimens

In response to these failures, Janssen convened a cross-disciplinary task force of scientists to identify the root cause of the problem and devise a solution. Appx10786-10789(786:3-789:4); Appx22747-22748. Inventor Dr. Vermeulen, in one of the most "complex" and "difficult" statistical challenges she faced in over 30 years of drug development, Appx10799-10800(799:4-800:17); Appx10812-10813(812:23-813:11), used a sophisticated technique called population pharmacokinetics to analyze Janssen's proprietary and unpublished clinical data, assess the factors leading to the Phase III failures, and simulate possible modifications of the failed dosing regimens, Appx10799-10802(799:4-802:1); Appx10810-10818(810:25-818:11); Appx22878-22972, at Appx22891; Appx22988-23014. Based on Dr. Vermeulen's modeling and simulations, the task force recommended an initial day 1 dose of 150 mg-eq. in the deltoid, followed by

maintenance doses of 25, 50, 100, or 150 mg-eq. in the deltoid or gluteal starting on day 8. Appx10796-10798(796:5-798:8); Appx23027-23029.

Dr. Gopal then designed two additional multi-million-dollar Phase III clinical trials—PSY-3006 and PSY-3007—to test the dosing regimens recommended by Dr. Vermeulen. Appx10820(820:4-22); Appx11066-11069(1066:8-1069:19); Appx22750-22818, at Appx22752. But in spring 2007, after the new trials had just begun, the results of the earlier PSY-3002 trial arrived. Appx10821-10823(821:14-823:2); Appx24819-24820. It was another failure, with paliperidone palmitate performing statistically worse than Risperdal Consta. *Id.*; Appx11086-11087(1086:21-1087:14). In a rare step, Dr. Gopal ordered the clinical trial sites to halt enrollment in the ongoing studies, stating that the PSY-3002 data showed the "current dosing regimen" for the ongoing studies was "not optimal" and would "have to be modified substantially." Appx24817. Dr. Gopal revised the PSY-3006 protocol to require a day-1 dose in the deltoid of 150 mg-eq., a day-8 dose of 100 mg-eq. into the deltoid, and maintenance doses of 50, 100, and 150 mg-eq. on day 36 and monthly thereafter. Appx11091-11092(1091:19-1093:21); Appx24834-24835. This became the patented and FDA-approved regimen.[2] Appx11106(1106:10-22).

[2] Teva's argument that the failure of the early Phase III trials was due to "using the wrong needle length," Br. 30, 64-65, has no evidentiary support. *Infra* at 62-63.

Meanwhile, inventor Dr. Mahesh Samtani refined Dr. Vermeulen's population pharmacokinetic model. Appx10797-10798(797:24-798:2); Appx11343-11344(1343:10-1344:18). Through sophisticated mathematical techniques, Dr. Samtani significantly improved the model's predictive power. Appx11349-11354(1349:1-1354:16); Appx11411(1411:5-11); Appx38715-38729. Using his new model, Dr. Samtani confirmed that the 150 mg-eq. day 1/100 mg-eq. day 8 deltoid dosing regimen was optimal for rapid and sustained efficacy. Appx11358-11360(1358:12-1360:13); Appx26817-26820.

Through modeling and simulation, Dr. Samtani also identified a dosing regimen for renally-impaired patients, Appx11388-11390(1388:3-1390:17), as well as recommendations for missed doses, and "windows" around the recommended dose timing, Appx11345-11346(1345:18-1346:8); Appx11381-11386(1381:8-1386:3); Appx38998-38999; Appx39003-39031. The FDA accepted Dr. Samtani's modelling—the first time such modelling was used to support drug approval. Appx11361-11363(1361:9-1363:4); Appx11389-11390(1389:17-1390:4); Appx11391(1391:13-21); Appx47967-47976.

4. Outside Experts Were Skeptical of the Claimed Dosing Regimens

The inventors' novel dosing regimens faced skepticism from outside experts steeped in the conventional wisdom of "start low, go slow." In February 2007, Janssen presented early findings of Dr. Vermeulen's population

pharmacokinetic analysis to a panel of outside experts. They thought Janssen's recommendation of an initial 150 mg-eq. dose was "risky" and pressed Janssen to "go for a lower [initial] dose." Appx11073-11076(1073:20-1075:16); Appx11082-11083(1082:3-1083:5); Appx20280-20283. Subsequently, the FDA responded to Janssen's New Drug Application by suggesting that Janssen offer a lower initiation dose of 75 mg-eq.—half the dose that the '906 patent claims. Appx11101-11102(1101:8-1102:21); Appx11376-11377(1376:1-1377:19); Appx20375-20377. Even after FDA approval, psychiatrists remained wary of Invega Sustenna's high-dose initiation regimen. Appx11108(1108:11-23); Appx11907-11908(1907:7-1908:8); Appx12426(2426:5-12); Appx49984.

5. The Claimed Dosing Regimens Achieved Rapid and Sustained Efficacy Without Oral Supplementation

The results of the PSY-3007 and PSY-3006 studies vindicated Janssen's faith in its unconventional approach. These studies confirmed that the new dosing regimens safely achieved rapid efficacy without oral supplementation, while also ensuring long-term efficacy. Whereas the earlier studies showed no efficacy for U.S. subjects and no rapid efficacy for anyone, PSY-3007, employing the new dosing regimens, showed rapid efficacy for the general patient population. Appx11098-11100(1098:3-1100:22); Appx39137-39155. PSY-3006 demonstrated that paliperidone palmitate was statistically non-inferior to Risperdal Consta, with

the raw data favoring Invega Sustenna. Appx11106-11107(1106:20-1107:25); Appx42048-42052.

Dr. Samtani's modeling confirmed that administration of Invega Sustenna in accordance with the '906 patent's claimed dosing regimens results in 84% of subjects reaching the therapeutic paliperidone blood concentration range within one week, a clinically significant achievement directly connected to the commercial success of Invega Sustenna. Appx11104-11106(1104:22-1109:9); Appx39036-39045, at Appx39041.

C. Invega Sustenna Is the Leading LAI Antipsychotic Due to the Claimed Dosing Regimens

Since its 2009 launch, Invega Sustenna has become by far the most commercially successful LAI on the market. It has accounted for more than 50% of the annual revenue generated by ***all*** LAI antipsychotic treatments in the United States every year since 2014. Appx12526-12531(2580:20-2585:22); Appx12782(2836:18-22); Appx56072-56073. By days of treatment, Invega Sustenna is more than twice as widely used as its closest second-generation LAI competitor. Appx12528-12529(2582:24-2583:18); Appx12781(2835:9-13); Appx56017-56018; Appx56039-56046. This is despite the existence of vigorous competition in the LAI marketplace. Appx12528(2582:1-13).

Invega Sustenna's commercial success derives in large part from the claimed dosing regimens and the rapid and sustained efficacy they provide.

Appx107-110; Appx11914-11916(1914:21-1916:14); Appx12542-12543(2596:1-2597:3); Appx12564(2618:2-15); Appx12798-12799(2852:17-2853:12). Invega Sustenna's LAI market share (30.9%) is vastly larger than that of short-acting (oral) paliperidone (1.0%), demonstrating that the features of the LAI drug product rather than the underlying molecule are responsible for its commercial performance. Appx12544-12546(2598:21-2600:20). These features—namely, a second-generation LAI that safely achieves rapid and sustained efficacy, without oral supplementation—are enabled by the claimed invention. Appx11914-11916(1914:21-1916:14); Appx12546-12547(2600:22-2601:3); Appx12564(2618:2-15).

D. The '906 Patent

On December 19, 2007, Janssen filed the first provisional application leading to the '906 patent. Appx20145; Appx152. At trial, the parties agreed to litigate five representative claims: claims 2, 10, 13, and multiple dependent claims 20-21 (as they depend from claims 1 or 8). Appx1061.

1. The Specification Discloses Improving Patient Adherence Through Rapid and Sustained Efficacy

The '906 patent's specification describes the invention's goals of improving patient adherence with an LAI that would ensure rapid and sustained efficacy. It explains that "up to 75%" of schizophrenia patients "have difficulty adhering to a daily oral treatment regimen," and that "[p]roblems with adherence,"

in turn, "often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies." Appx159(1:50-57). The inventors sought to solve this problem by developing a LAI paliperidone palmitate injection that could "provide sustained plasma concentrations of paliperidone when administered once monthly," while also ensuring "rapid attainment of potential therapeutic concentrations." Appx159(1:58-61); Appx160-161(4:64-5:5). But "after the data was analyzed from [early] clinical trials . . . it was discovered that the absorption of paliperidone from these injections was far more complex than was originally anticipated." Appx159(1:64-67). An "extensive analysis of the clinical data" led to the development of the claimed dosing regimens, which "facilitate patients' attaining a rapid therapeutic concentration of paliperidone." Appx160-161(4:64-6:16).

2. Claim 2: The Dosing Regimen That Emerged from Janssen's Development Crisis

Representative claim 2, which depends from claim 1, recites a dosing regimen for administering a sustained release formulation of paliperidone palmitate to treat a patient with schizophrenia, schizoaffective disorder, or schizophreniform disorder. As Teva acknowledged at trial, claim 2 is a "general" dosing regimen, Appx10201-10202(201:10-202:1), intended for the "general population of schizophrenia patients," Appx10325(325:18-326:3). *See infra* at 20-21. The claim

does not depend upon individual patient characteristics (such as body weight or previous dose of oral medication), but rather provides a uniform loading dose regimen suitable for any patient with one of the claimed diseases (other than those with renal impairment).

Under claim 2, a patient is administered paliperidone palmitate according to a standardized initiation regimen consisting of an initial loading dose of 150 mg-eq. into the deltoid on day 1, followed by a second loading dose of 100 mg-eq. into the deltoid on day 6-10. Thereafter, patients are administered monthly (±7 days) maintenance doses of 25-150 mg-eq. into the deltoid or gluteal muscle.

As both parties' experts agreed, claim 2 embodies the specification's stated objectives of achieving "rapid" and "sustained" efficacy. Appx159(1:58-61); Appx 160-161(4:64-5:5). The two loading doses of claim 2 provide for rapid efficacy, and the maintenance doses provide sustained efficacy. Appx10468-10470(468:13-470:13); Appx11473-11474(1473:21-1474:13).

3. Claims 10 and 13: The Renal Impairment Dosing Regimens

Representative claims 10 and 13, depending from claims 8 and 11, set forth separate dosing regimens for renally-impaired patients. Claim 10 recites a dosing regimen for a renally-impaired patient consisting of two loading doses "of from about" 75 mg-eq. into the deltoid on day 1 and day 6-10, followed by monthly (±7 days) maintenance doses of 25-75 mg-eq. Claim 13 recites two

loading doses "of from about" 75 mg-eq. into the deltoid on days 1 and 8, followed by monthly (±7 days) maintenance doses of 25-50 mg-eq.

4. Claims 20 and 21: The Dosing Regimen and Formulation

Representative claims 20 and 21 are multiple dependent claims depending from claims 1, 4, 8, or 11, but litigated only as they depend from claims 1 and 8. Appx1061. They recite precise characteristics of the paliperidone palmitate formulation, including specifying that the "average particle size (d50)" of paliperidone palmitate is "from about 1600nm to 900nm." This specific particle size range is not disclosed in the prior art. *See infra* at 25-26.

E. District Court Proceedings

Teva and Mylan filed Abbreviated New Drug Applications ("ANDAs") for generic versions of Invega Sustenna, leading to the underlying district court litigation. The Teva action proceeded to trial first, and Mylan agreed to be bound by the judgment. Appx49.

1. Claim Construction and Infringement

Prior to trial, Janssen and Teva agreed to forego claim construction proceedings. Appx1895. Teva (and later Mylan) stipulated to infringement of all claims. Appx1050-1052; Appx70001-70004.

2. Teva's Obviousness Defenses

At trial, Teva's witnesses and counsel repeatedly acknowledged that claims 2 and 20-21 are "general" dosing regimens intended for the "general population" of schizophrenia patients. Teva's principal obviousness expert, Dr. Wermeling, referred to these claims as the "***general*** . . . dosing regimens" and testified that they recited the "standard or full dose for ***general*** patients who have schizophrenia." Appx10201-10202(201:10-202:1).[3] Teva's trial counsel described claim 2 as "the regimen that's claimed in the '906 patent for the ***general population*** of schizophrenia patients," Appx10325-10326(325:18-326:3), termed claims 2 and 20-21 the "***general*** dosing regimens," Appx10327-10328(327:22-328:3), and observed that claim 2 recites a dosing regimen for the "***general*** patient," Appx10335(335:8-13); *see also* Appx1547; Appx56159; Appx56176; Appx56226.

With respect to the "general" dosing-regimen claims, Teva argued that a POSA would have been motivated to combine three primary references—the '544 patent, WO 384, and the 548 Protocol—with nine secondary references to arrive at the claims with a reasonable expectation of success. Appx65; Appx68-69 & n.18. Specifically, Teva contended that desires "to avoid oral supplementation, ***reach therapeutic plasma levels faster***, and reduce the risk of relapse" and

[3] All emphases added unless otherwise noted.

"***accelerate the onset of effect***" would have motivated a POSA. Appx1426; Appx1548; Appx10311(311:18-23).

With respect to claims 10 and 13, Teva contended that a POSA would "[k]now to [c]ut [a]ny [g]eneral [d]osing [r]egimen in [h]alf for [r]enally-[i]mpaired [p]atients." Appx56297; Appx1556-1557. Teva specified that a POSA would have been motivated to reduce doses by 50% for patients with "mild renal impairment." Appx10332-10333(332:1-333:12); Appx56240.

3. Teva's "d50" Indefiniteness Defense

At trial, Teva asserted that the particle size ("d50") limitation in claims 20-21 was indefinite. Although Teva's expert Dr. Block noted (correctly) that there are different techniques for measuring particle size, Appx10589-10590(589:4-590:13), he acknowledged that any differences between these techniques "may or may not be significant," depending on the facts, Appx10630(630:14-25).

F. The District Court's Decision

After a twelve-day trial, the district court issued a comprehensive 95-page opinion, in which it carefully weighed the record evidence and the credibility of the witnesses and concluded that Teva had failed to meet its burden of proving invalidity by clear and convincing evidence.

1. Nonobviousness

a. No Motivation to Modify the 548 Protocol

With respect to obviousness, the district court observed that "Teva's prior art combinations all involve modifying" the 548 Protocol, the only reference that "discusses a dosing regimen for initiating treatment of paliperidone palmitate." Appx69. The 548 Protocol is a "two-page summary protocol of Janssen's unsuccessful PSY-3003 clinical trial." Appx70. It was undisputed that this reference was just a "protocol without any results," lacking "any safety or efficacy data." Appx71; Appx10423(423:20-21); Appx10471(471:10-14).

As the court found, Dr. Sinko "credibly testified" that a POSA would not have been motivated to modify the 548 Protocol to achieve the claimed dosing regimens in the absence of clinical data to support such modifications. Appx72. In contrast, Dr. Wermeling "appeared to rely on impermissible hindsight," which he conceded at his deposition. Appx72-73 n.25. Although Dr. Wermeling "attempted to disavow" his deposition testimony at trial, as to hindsight and other issues, the court was unpersuaded, finding that "Dr. Wermeling's testimony has credibility issues." *Id.*

The district court rejected Dr. Wermeling's testimony that a POSA would have been motivated to modify the 548 Protocol to "accelerate the onset of effect" (based on the teachings of Ereshefsky) and to treat the "life-threatening"

condition of "acute" agitation. Appx73; Appx90 n.31. This testimony was "contradicted" by Teva's own medical expert, Dr. Kahn. Appx73. The "inconsistency" between Teva's experts' testimony further "belie[d] Defendant's theory of motivation." *Id*.

b. No Motivation to Arrive at the Individual Elements of the Claims

Having found that Teva failed to prove motivation to modify the 548 Protocol at all, the district court then addressed Teva's arguments regarding each of the individual elements of the claims.

Deltoid administration of loading doses. With respect to the deltoid injection site, the court noted that Teva did not rely on any prior art concerning paliperidone palmitate. Appx74-76.[4] The court was not persuaded by Dr. Wermeling's testimony that two references, Goodman and Gibaldi, "would motivate a POSA to arrive at the claimed regimens because they teach that deltoid injections lead to faster absorption than gluteal injections." Appx75-77. Dr. Wermeling ignored Goodman's teaching—"persuasively conveyed" by Dr. Sinko—that for depot formulations such as those claimed in the '906 patent, the

[4] Appellants refer to references disclosing deltoid injections of paliperidone palmitate, Br. 17-18, but Teva did not rely on any of these references in its obviousness theories before the district court, Appx68-69 & n.18; Appx1063, and has therefore waived reliance on them, *Gant v. United States*, 417 F.3d 1328, 1332 (Fed. Cir. 2005).

site of the injection was irrelevant to absorption. Appx76; Appx11533-11536(1533:23-1536:15). Similarly, Dr. Wermeling "admitted" ignoring Gibaldi's teaching that depot injections are not suitable for initiating therapy. Appx77; Appx10472(472:2-9).

The district court also rejected Teva's argument that general familiarity with or "patient preference" for deltoid injections would have led a POSA to the claimed invention. Appx77-78. The prior art recommended administering LAIs in the gluteal rather than deltoid muscle because deltoid injections "cause[] discomfort and pain at the injection site." Appx78 (quoting Appx14144). And even if patient preference might sometimes lead to "using deltoid administration on an individualized basis," this would not lead to the "generalized dosing regimen" of the claims, Appx78, which comprise "a precise combination of dose amounts, dose timing, sites of administration, and particle size," Appx68.

Unequal loading doses. Teva relied on Ereshefsky and Karagianis to suggest that a POSA would have modified the 548 Protocol to arrive at the unequal loading doses of claim 2. The district court credited Dr. Sinko's testimony that these references were not germane because they involved "different drugs and different formulations" than paliperidone palmitate. Appx78-79.

Ereshefsky and Karagianis also did not teach dosing "according to a protocol-dosing regimen" as in the '906 patent, instead using "individualized" or "personalized" approaches to dosing (based on a specific patient's prior dosage or specific symptoms). Appx79; Appx11577(1577:4-12); Appx11569-11570(1569:6-1570:9). Teva failed to show that these approaches would have led a POSA to the "generalized" combination of dose amounts, dose timing, and injection sites required by the claims. Appx79.

Finally, the district court found, Teva's references "do not disclose unequal loading doses" at all. Appx80. Ereshefsky teaches equally "divided" loading doses of haloperidol decanoate, not unequal ones, and Ereshefsky's dose reduction does not occur until the "second and third months" of treatment—*i.e.*, maintenance doses, not loading doses. Appx80.

Particle size. At trial, Teva conceded that the '544 patent was the only reference to disclose particle size for a paliperidone palmitate LAI. Appx85-86.[5] The district court credited Dr. Sinko's testimony that, although the '544 patent discloses one example of a formulation (Formulation B) falling within the claimed particle size distribution, the reference as a whole "teaches away" from using

[5] Contrary to Appellants' assertion, Br. 14, the district court was correct that WO 384 "describ[es] a new process for creating raw paliperidone palmitate crystals." Appx68 n.19. It discloses the final formulation only in passing, with no information about particle size. Appx13300-13321.

Formulation B by teaching that this formulation lacked desirable characteristics and was not chosen for further investigation. Appx84-85; Appx11529-11530(1529:24-1530:8); Appx11784-11785(1784:7-1785:13).

Renal impairment. With respect to claims 10 and 13, Teva relied on the same references on which it unsuccessfully relied to show the supposed obviousness of the general dosing regimens. Appx81. The district court rejected Dr. Wermeling's testimony that additional references related to dosing oral paliperidone for renally-impaired patients taught a "50 percent dose reduction from the maximum dose for patients with mild renal impairment." *Id*. The district court found that these references did not teach a "straight" dosing reduction of oral paliperidone, and that claims 10 and 13 do not reflect a "straight" dosing reduction from the allegedly obvious general dosing regimen of claim 2. Appx82-83.

c. No Reasonable Expectation of Success

The district court also found that Teva failed to establish a reasonable expectation of success. Appx86-90. The court found that "developing treatment initiation regimens using LAIs" was unpredictable, and that the prior art contained no clinical data that would have helped a POSA assess how a multi-dose treatment regimen would "perform in patients." Appx87-88. The "difficulty the Janssen inventors encountered" in developing a safe and effective dosing regimen and the skepticism of outside experts reinforced this finding. Appx88-89. Furthermore, "a

POSA would not have had a reasonable expectation of successfully initiating treatment with LAI loading doses" in view of prior-art teachings that LAIs are typically used for "maintenance treatment rather than initiation of therapy" and the fact that all of the LAI antipsychotics available prior to Invega Sustenna were dosed according to a "start low, go slow" approach. Appx89 (quoting Appx14134).

d. Objective Indicia of Nonobviousness

The court found that objective evidence supported nonobviousness, and that there was a nexus to the asserted claims because the evidence was "linked to the high loading dose deltoid injections and subsequent maintenance injections described in the '906 Patent." Appx94. This objective evidence rebutted "any alleged presumption of obviousness" urged by Teva. Appx116.

Unexpected results. The district court found that the asserted claims led to the unexpected outcome of a "second-generation LAI that successfully treated schizophrenia . . . without the need for oral supplementation." Appx95. The claimed dosing regimens were contrary to the "conventional wisdom" of "start low and go slow," which had suggested that LAIs were "'indicated for maintenance treatment rather than initiation of therapy.'" Appx95-96 (quoting Appx20094). The history of the invention further demonstrated that the claimed dosing regimens unexpectedly succeeded where the prior art failed. Appx96-97.

Skepticism. Recommendations by an outside panel of experts and by the FDA that Janssen use a lower initial dose for Invega Sustenna evidenced skepticism of the claimed dosing regimens. Appx97-98. The court rejected Teva's argument that the FDA's feedback was merely "advice" and not skepticism, relying on this Court's decision in *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019).

Praise. Several trade publications showed praise of the claimed inventions. Appx100-102. One reported that Invega Sustenna (alone among LAIs) had been shown superior to oral antipsychotics, a result attributed to "better adherence rates." Appx100-101 (quoting Appx20542). Others specifically "confirm[ed] the importance of Invega Sustenna's high initial loading doses." Appx101; Appx20567; Appx20544.

Copying. The district court accorded some "limited weight" to the fact that Teva copied the particle size recited in claims 20-21, given that Teva was not required to copy the claimed particle size, but did so anyway. Appx102-103.

Long-felt need and failure of others. Before Invega Sustenna, the district court found, LAIs "had significant limitations," notably requiring oral supplementation upon initiation because they did not achieve rapid efficacy. Appx104-105. The "'906 Patent fulfilled this long-felt need." Appx105.

Commercial success. The record "establish[ed] that the benefits of the patented dosing regimens contributed to Invega Sustenna's success on the market," a point that Teva's economics expert "did not refute." Appx108. And Teva failed to show that alleged "blocking patents" defeated commercial success, both because it strategically chose not to present Dr. Wermeling's testimony on the alleged patents, and because the trial evidence showed that molecule and formulation patents did not deter competitors from attempting to enter the market with competing LAIs. Appx111-114.

2. Teva's "d50" Indefiniteness Challenge

The district court rejected Teva's argument that the term "d50" in claims 20-21 is indefinite because d50 (*i.e.*, median particle size) can be measured in different ways. Appx127-135. The court canvassed this Court's case law and concluded (correctly) that "differing methods of measuring and representing d50 particle size must lead to meaningfully different results in order to render Claims 20 and 21 indefinite." Appx131-132. The district court found, based on evidence and testimony, that "the different methods of measuring and expressing d50 were likely to produce substantially similar values" in the context of the '906 patent. Appx134. The court therefore concluded that Teva had failed to prove indefiniteness.

SUMMARY OF THE ARGUMENT

The district court correctly concluded that Teva failed to prove obviousness or indefiniteness by clear and convincing evidence.

The district court properly found that Teva failed to prove motivation to modify the prior art to arrive at claims 2 and 20-21 with a reasonable expectation of success. The court did not misinterpret these claims but rather recognized, as Teva acknowledged at trial, that they are intended for the "general population of schizophrenia patients." Appx10325-10326(325:18-326:3). When the court found that a desire to safely achieve rapid efficacy would not have motivated a POSA to arrive at the general dosing-regimen claims, it was simply rejecting Teva's obviousness theories, which is not legal error. *See, e.g.*, *Immunex*, 964 F.3d at 1066-67; *Intelligent Bio-Sys.*, 821 F.3d at 1368. And when the court found that a POSA would not have had a reasonable expectation of success in treating a schizophrenia patient given the absence of relevant data from prior-art clinical studies of the schizophrenia patient population, it was correctly finding facts about what would have been "important" to a POSA. *See, e.g.*, *Eli Lilly*, 8 F.4th at 1347.

In finding that Teva failed to prove obviousness, the district court did not "overemphasize the importance of published articles," *KSR*, 550 U.S. at 418, or disregard the "perspective of a skilled artisan." Br. 48. To the contrary, the court

relied extensively on the testimony of skilled scientists to determine what teachings a POSA would have drawn from the prior art. The district court correctly found that Teva's obviousness expert, Dr. Wermeling, had "credibility issues." Appx72-73 n.25. It properly discredited his testimony as to alleged motivation to modify the 548 Protocol (on which all of Teva's obviousness theories relied), and as to the alleged obviousness of the individual elements of the claimed dosing regimens.

The district court correctly rejected Teva's argument that a motivation to treat patients with mild renal impairment would have led a POSA to claims 10 and 13. In doing so, the court did not add elements to the claims but simply rejected Teva's obviousness case. Furthermore, since Teva's obviousness case as to claims 10 and 13 relies on the same references as the general dosing regimen claims, it fails for the same reasons.

The district court correctly concluded that Teva failed to prove the indefiniteness of claims 20-21, containing particle-size limitations. The court recognized that the existence of different measurement techniques does not render a claim indefinite unless the "different measurement techniques in fact produce[] significantly different results." *Takeda*, 743 F.3d at 1367. The court correctly found that Teva failed to establish this. Appellants' argument to the contrary overlooks the clear record evidence that different measurement techniques repeatedly led to the same results for paliperidone palmitate particle size, and that

the one instance where the results appeared to differ arose from an equipment defect that was swiftly reconciled.

ARGUMENT

I. STANDARD OF REVIEW

"On appeal from a bench trial, this court reviews the district court's conclusions of law de novo and findings of fact for clear error." *MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1266 (Fed. Cir. 2013). Under clear error review, this Court "'gives great deference to the district court's decisions regarding credibility of witnesses,'" because "'only the trial judge can be aware of the variations in demeanor and tone of voice that bear so heavily on the listener's understanding of and belief in what is said." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171 (Fed. Cir. 2006) (citations omitted).

II. THE DISTRICT COURT CORRECTLY CONCLUDED THAT TEVA FAILED TO PROVE OBVIOUSNESS

The district court's "legal conclusion about obviousness" is reviewed de novo and its "underlying factual findings" are reviewed "for clear error." *HZNP Meds. LLC v. Actavis Lab'ys UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019). A party challenging a district court's determination of nonobviousness faces "a difficult burden" on appeal, as it must both overcome the presumption that issued patents are valid and establish that the district court erred. *Cadence Pharms., Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1375 (Fed. Cir. 2015).

Seeking to avoid the burden of showing clear error, Appellants contend that the district court erred as a matter of law by requiring Teva to prove the obviousness of unclaimed elements of the asserted claims and by misapplying *KSR*. Br. 35-38. That is incorrect. The district court's conclusions on obviousness constituted a rejection of the case Teva tried and were firmly grounded in the testimony and documentary evidence presented at trial. The court's conclusions were correct and should be affirmed.

A. For the Claims Directed at a General Dosing Regimen (Claims 2 and 20-21), the District Court Did Not Require Teva to Prove the Obviousness of Unclaimed Elements

Appellants contend that the district court "required Teva to prove the obviousness of unclaimed elements" of claims 2 and 20-21 when it "criticized Teva's evidence for failing to show obviousness of '***generalized***' dosing regimens that are ***safe*** and ***rapidly effective*** for ***a majority of patients***." Br. 37 (emphases original). They further contend that this supposed "legal error," Br. 39, led the court to mistakenly "criticize[] the prior art for lacking ***clinical data*** the court believed necessary to make a 'generalized' dosing regimen obvious." Br. 42, 43-45. This argument fails.

Contrary to Appellants' contention, the district court did not interpret claims 2 and 20-21 to require treatment of more than "a psychiatric patient" when it referred to them as "generalized" dosing regimens. Br. 40-41. The court clearly

acknowledged that "the claimed invention . . . consists of a precise combination of dose amounts, dose timing, sites of administration, and particle size, designed for ***a patient*** in need of treatment for schizophrenia." Appx68. By using the term "generalized," the district court accurately recognized that the claims 2 and 20-21 recite a precise combination of dosing elements that are intended to treat the general population of schizophrenia patients with a "uniform" loading dose regimen that is not dependent on individual patient characteristics such as body weight or prior treatment. Appx68-69 & n.20. It did not construe the claims to require treatment of multiple patients.

As described above, Teva's own witnesses and counsel used similar terminology to describe claims 2 and 20-21. *Supra* at 20-21. Dr. Wermeling testified that these claims recite "the ***standard*** or full ***dose*** for ***general*** patients who have schizophrenia." Appx10201(201:10-16). Teva's trial counsel described claim 2 as "the regimen that's claimed in the '906 patent for the ***general population*** of schizophrenia patients." Appx10325-10326(325:18-326:3). Indeed, the slide summarizing Dr. Wermeling's ultimate opinion on the obviousness of claims 2 and 20-21 was titled: "The ***General Dosing Regimen Claims*** Are Obvious in View of the Prior Art." Appx56226. The district court properly concluded that Teva failed to meet its burden of proving this.

1. The District Court Correctly Rejected Teva's Theory That a Desire for Rapid Efficacy Would Have Motivated a POSA to Arrive at the Claimed Inventions

As described above, Teva contended at trial that a POSA's motivation to modify the prior art would have arisen from a desire to achieve rapid efficacy. *Supra* at 20-21. Dr. Wermeling testified that a POSA would have been motivated to develop loading dose regimens to "accelerate the onset of effect." Appx10311(311:18-23). He opined that a POSA would have selected 150 mg-eq. as the first loading dose because "you would be motivated to use the maximum effective and safe dose" to address "acute[] agitat[ion]." Appx10321(321:11-16). He further opined that a POSA would have administered loading doses in the deltoid muscle in light of Gibaldi's and Goodman's alleged teachings that the deltoid provides a "faster rate of absorption" than the gluteus. Appx10324(324:14-23). As Teva summarized the argument in post-trial briefing, "a POSA would have been motivated to develop loading dose regimens . . . to avoid oral supplementation, reach therapeutic plasma levels faster, and reduce the risk of relapse." Appx1426.

The district court did not commit legal error in rejecting Teva's theory of motivation. Appx73-77; Appx90 n.31. When a patent challenger argues that a particular objective would have motivated a POSA to arrive at the claimed invention, the factfinder may consider and reject that argument, regardless whether

the alleged objective is expressly required by the claim. In *Intelligent Bio-Systems,* for example, this Court upheld the PTAB's finding of nonobviousness when the petitioner failed to show that a desire to meet a "quantitative deblocking requirement" would have motivated a POSA to arrive at the invention. 821 F.3d at 1368. The Court emphasized that the claims "***do not require quantitative deblocking at all***." *Id*. But because the petitioner argued that "quantitative deblocking" would have motivated a POSA, the PTAB "was justified in finding" that the petitioner failed to meet its burden of proof. *Id.*

Similarly, in *Immunex*, this Court affirmed the district court's finding that a POSA would have been deterred from combining prior art references to treat inflammation. 964 F.3d at 1066. The Court rejected Sandoz's argument that "this was legal error because the claims are not directed to treatment of any disease or condition," pointing out that "Sandoz focused on these therapeutic goals as evidence of motivation." *Id.* This was true even though Sandoz had also presented alternative motivations in post-trial briefing. *Id.* at 1066-67. "The focus of Sandoz's motivation to combine argument remained the therapeutic benefits of the claimed invention, and it was not error for the district court to frame its analysis accordingly." *Id.* at 1067; *see also Institut Pasteur v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) (where alleged motivation to combine was to cleave DNA

"of a living animal cell," prior-art teachings regarding toxicity were relevant to obviousness, even though patent did not expressly require cell viability).

The cases on which Appellants rely, in contrast, deal with unclaimed motivations on which the patent challenger did ***not*** rely. In *Canfield Sci., Inc. v. Melanoscan, LLC*, 987 F.3d 1375, 1383 (Fed. Cir. 2021), the PTAB erred by reading into the claims a limitation "as to the location of the subject being imaged," ignoring the petitioner's argument that the patent was broad enough to cover a different location that would have been obvious. In *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 962-63 (Fed. Cir. 2014), the district court erred when it limited its analysis of a patent covering a class of compounds to a single subset of compounds the patentee (not the challenger) had focused on. Similarly, in *Senju Pharmaceutical Co. v. Lupin Ltd.*, 780 F.3d 1337, 1347 (Fed. Cir. 2015), the Court rejected the argument of the patentee (not the challenger) that the prior art did not "disclose anything about corneal permeability" because corneal permeability was "not a limitation" of the claims.

None of these cases undermines the principle that a factfinder may reject the patent challenger's theory of motivation regardless of whether the alleged motivation is expressly required by the claims. The district court properly applied that principle here.

2. The District Court Correctly Found That a POSA Would Have Had No Reasonable Expectation of Success in the Absence of Prior-Art Clinical Data

Appellants argue that the district court erred when it found a POSA would have lacked a reasonable expectation of success because (in part) there was no prior-art clinical data showing safety and efficacy in a general population of schizophrenic patients. Br. 42-45. Appellants' suggestion that the absence of population-level clinical data is irrelevant to obviousness finds no support in the case law, the trial record, or the '906 patent.

Appellants do not dispute that, although they do not expressly require a clinical result, the asserted claims are directed to the purpose of treating patients with schizophrenia. *See* Appx174-175 (reciting dosing regimens for "a psychiatric patient in need of treatment for schizophrenia"); *Eli Lilly*, 8 F.4th at 1340-43 (method-of-treatment claims recited "purpose" of treating migraine symptoms though they did "not ***require***" a "clinical result") (emphasis original). Nor can Appellants dispute that safety and efficacy are relevant to a reasonable expectation of successful treatment. *See Eli Lilly*, 8 F.4th at 1346-47 (lack of prior-art efficacy data relevant to reasonable expectation of success); *see also Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc*., 18 F.4th 1377, 1381-82 (Fed. Cir. 2021) (method-of-treatment claim not obvious where POSA "would have had no expectation" that claimed dosage would be safe); *OSI Pharms., LLC v. Apotex Inc.*,

939 F.3d 1375, 1383 (Fed. Cir. 2019) (no reasonable expectation of success for method-of-treatment claim where "the asserted references do not disclose ***any*** data or other information about erlotinib's efficacy"). Indeed, as discussed above, Teva itself argued that a desire for rapid efficacy would have motivated a POSA to arrive at the asserted claims. *See Institut Pasteur*, 738 F.3d at 1346 ("obviousness generally requires that a skilled artisan have reasonably expected success in achieving [the] goal" that "motivate[s]" the claimed combination).

Instead of disputing the relevance of safety and efficacy, Appellants contend that the untested dosing regimens of the 548 Protocol were "thought to be safe and effective." Br. 41. But the presence or absence of a reasonable expectation of success is a question of fact. *Teva*, 18 F.4th at 1380-81. The district court was correct, and certainly not clearly erroneous, to find that, given the absence of clinical data in the prior art, a POSA would have lacked a reasonable expectation of success in treating a patient with the claimed dosing regimens. Appx86-90; *supra* at 26-27.

No case law supports Appellants' argument that a patent must claim efficacy in a general patient population for clinical data to be relevant to reasonable expectation of success. Br. 42-45. *Yeda Research & Development Co. v. Mylan Pharmaceuticals Inc.*, 906 F.3d 1031 (Fed. Cir. 2018), on which Appellants rely (Br. 45), does not establish that point. It simply rejects the argument that "a

reasonable expectation of success is ***categorically impossible*** in the absence of a pk/pd [pharmacokinetic/ pharmacodynamic] profile." *Id.* at 1043. In *Yeda*, the prior art was replete with relevant clinical data (other than pk/pd data), including "clinical studies that taught the effectiveness" of the drug. *Id.* Furthermore, the factfinder "credited testimony" from the petitioner's expert that POSAs "considered [the drug] to be a 'forgiving drug'" whose efficacy could be predicted from the prior-art clinical studies. *Id.* at 1043-44. In short, *Yeda* holds that a reasonable expectation of success ***can*** be established in the absence of certain types of clinical data. It does not remotely suggest that clinical data is categorically irrelevant to the inquiry.

To the contrary, the case law consistently holds that the absence of clinical data can support nonobviousness of claims directed at treatment. *See, e.g.*, *Eli Lilly*, 8 F.4th at 1347 (noting that "if the prior art had included efficacy data . . . that fact would have been important in the obviousness analysis, ***but no such data were disclosed***") (emphasis original); *OSI*, 939 F.3d at 1383-84 (method-of-treatment claim not obvious where "the asserted references do not disclose any data or other information about erlotinib's efficacy"); *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1061 (Fed. Cir. 2019) (method-of-treatment claim not obvious where "there were no clinical trial data on everolimus as an anti-cancer agent").

Indeed, despite Appellants' arguments on appeal, there was no serious dispute at trial that clinical studies were relevant to obviousness. As the record showed, the efficacy of a treatment for schizophrenia—whose biological mechanisms are not well-understood and is therefore defined by its symptoms, Appx10083-10084(83:2-84:21)—can only be evaluated by comparing symptom improvement in a study population to that of a placebo or control group. Appx10774-10775(774:18-775:16). And Dr. Wermeling, who touted that he had "performed probably over 100 clinical studies in [his] career," Appx10196(196:14-18), testified extensively about clinical studies when discussing the expectations of a POSA, Appx10205-10207(205:22-207:23); Appx10290-10293(290:18-293:15); Appx10340-10341(340:12-341:16).

In particular, Dr. Wermeling testified that the "state of the art prior to the filing date of the '906 patent" included "Phase I studies" to determine the "pharmacologic profile and the relative tolerability of the medicine in the subjects," "Phase II studies" to study the "***target patient population*** who have the disease or the medical problem of interest," and "Phase III studies" in a "***larger patient population***" to "confirm[] that the doses used in Phase II studies" are "safe and effective for prescribing if the drug gets approved." Appx10205-10207(205:16-207:23). The relevance of population-level clinical data to a POSA was therefore undisputed.

Moreover, and contrary to Appellants' contention (Br. 43), the patent's specification makes abundantly clear that the claimed inventions were informed by clinical studies of the schizophrenia population. *See, e.g.*, Appx161(6:41-44) (referring to the "***patient population***" contemplated by the patent). The specification teaches that an "***extensive analysis of the clinical data***" led to the discovery of the claimed dosing regimens that "facilitate ***patients'*** attaining a rapid therapeutic concentration of paliperidone." Appx160-161(4:64-6:15). The patent then devotes multiple pages to clinical studies providing pharmacokinetic, safety, and efficacy data underlying the claimed inventions. Appx166-174(16:59-31:50).

The district court's finding of no reasonable expectation of success is overwhelmingly supported by the trial record. Here, unlike in *Yeda*, there were ***no*** data of any sort from prior-art clinical studies about a paliperidone palmitate LAI.[6] Appx72; Appx88. Contrary to *Yeda*, the credible expert testimony was that a POSA would ***not*** have had a reasonable expectation of success in the absence of

[6] In a footnote, Appellants cite Kramer, which they contend contains prior-art clinical data. Br. 29 n.4. But Teva failed to disclose Kramer at any point during the district court proceedings. Appx92 n.35. This was not surprising, since in parallel Canadian litigation, the court (upholding the validity of the '906 patent's Canadian counterpart) found that Kramer was ***not*** prior art because "***there is no evidence that it was presented***, or at least what was presented" publicly. Appx1739(961:22-28); Appx1794. In any event, "arguments raised in footnotes are not preserved," *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1320 (Fed. Cir. 2006), so Kramer has no place in this appeal.

such data. *Id.*; *supra* at 41. And the prior art provided no reason to expect success, as the claimed dosing regimens went against the "traditional dosing paradigm" of starting low and going slow. Appx89-90.

Finally, the real-world evidence showed that the inventors relied heavily on large clinical studies of the schizophrenia population and sophisticated analysis thereof, and that they experienced numerous unexpected setbacks before ultimately discovering the claimed dosing regimens. *Supra* at 9-13. This evidence provided yet more support for the district court's finding of no reasonable expectation of success. Appx88-89. *See, e.g.*, *Endo Pharms. Inc. v. Actavis LLC*, 922 F.3d 1365, 1377 (Fed. Cir. 2019) (finding of no reasonable expectation of success "supported by the fact that the inventors . . . engaged in extensive experimentation, involving much failure" to arrive at invention).

B. The District Court Properly Considered the Evidence from the Perspective of a Skilled Artisan in Assessing Obviousness

Appellants argue that the district court misapplied *KSR* by "limiting the prior art to its explicit content" and "failing to take account of the inferences and creative steps a POSA would take." Br. 5, 48-50. That is the opposite of what the district court did. The court relied extensively on the trial testimony of skilled scientists regarding what the prior art taught. The court simply found Janssen's evidence more credible than Teva's. This was not clear error.

Appellants are correct that under *KSR* and this Court's precedents, "prior art 'must be considered not only for what it expressly teaches, but also for what it fairly suggests'" to a skilled artisan. Br. 49 (quoting *Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1049 (Fed. Cir. 2019)). But what the prior art suggests to a POSA is a question "reserved for the finder of fact" that "requires consideration of all the facts" in the record. *Arctic Cat Inc. v. Bombardier Recreational Prods*., 876 F.3d 1350, 1360 (Fed. Cir. 2017); *Trimed, Inc. v. Stryker Corp*., 608 F.3d 1333, 1341 (Fed. Cir. 2010). *KSR*'s caution against "rigid" analysis is not a one-way ratchet that can only support a conclusion of obviousness. Rather, the "prior art, skill, and knowledge of an ordinary artisan" may "provide reasons ***not*** to combine" and that too is "a question of fact." *Arctic Cat*, 876 F.3d at 1360.

It is Appellants' brief, not the district court's decision, that ignores the perspective of skilled scientists, urging this Court to adopt a simplistic reading of the prior art that is not supported by the trial record. The district court properly considered the testimony of skilled artisans and made credibility determinations and other factual findings that are not clearly erroneous.

1. The District Court Correctly Found No Credible Motivation to Modify the 548 Protocol

Appellants largely ignore the district court's primary reason for concluding that Teva failed to prove obviousness: Teva "fail[ed] to adequately

explain why a POSA would modify the '548 Protocol's teachings" to arrive at the claimed dosing regimens. Appx70-74. This finding was correct.

Dr. Sinko "credibly testified" that nothing in the prior art or a POSA's knowledge would teach that the 548 Protocol needed to be modified or, if so, how to modify it, since the prior art contained no information or data regarding the performance of the 548 Protocol. Appx72. Meanwhile, Teva's expert Dr. Wermeling relied on "impermissible hindsight." Appx72-73 n.25. Indeed, Dr. Wermeling admitted to using hindsight during his deposition, testifying that he used the asserted claims as a roadmap to find obviousness. *Id.*; Appx10357-10360(357:9-360:18). His attempt to disavow that testimony at trial was one reason the district court concluded Dr. Wermeling had "credibility issues." Appx72-73 n.25.

The district court also discredited Dr. Wermeling's testimony that "motivation to modify the '548 Protocol . . . can be derived from Ereshefsky's teachings about high loading doses and a desire to use LAIs to treat 'acute life-threatening circumstances.'" Appx73. The court found this testimony unpersuasive because Ereshefsky was inapposite (*see infra* at 50) and because Dr. Wermeling's testimony about "acute life-threatening circumstances" was "contradicted by the testimony" of Teva's medical expert Dr. Kahn, who testified that LAIs "don't work fast enough" to be used in emergencies. *Id*. This

"inconsistency between the experts' testimony belies Defendant's theory of motivation." *Id.*

Appellants wisely do not challenge the district court's credibility findings on appeal, since "[c]ourts of appeals cannot reweigh a district court's assessment of witness credibility." *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1341 (Fed. Cir. 2021). But this leaves the core factual basis for the district court's nonobviousness determination uncontested. "Motivation to combine is a question of fact." *Neptune*, 921 F.3d at 1375. The district court's well-founded credibility findings about the trial witnesses—all of whom were skilled artisans—should not be disregarded under the guise of giving proper effect to the "[p]erspective of a [s]killed [a]rtisan." Br. 48; *see, e.g.*, *Impax Lab'ys Inc. v. Lannett Holdings Inc*., 893 F.3d 1372, 1381-82 (Fed. Cir. 2018) (affirming nonobviousness determination where "court found Appellees' experts more credible than [Appellant's]"); *Senju*, 780 F.3d at 1351 (affirming obviousness determination where court's "analysis rests largely on a determination that Lupin's experts were more credible than Senju's experts"); *Braintree Lab'ys, Inc. v. Novel Lab'ys, Inc*., 749 F.3d 1349, 1359 (Fed. Cir. 2014) (affirming nonobviousness determination where Appellant "relies on expert testimony which the district court found to be less credible"); *Celsis In Vitro, Inc. v. CellzDirect, Inc*., 664 F.3d 922, 929 (Fed. Cir. 2012) (affirming nonobviousness determination because "district

court did not find the testimony of [patent challenger's] experts . . . credible" and "[t]his court defers to such credibility determinations").

2. The District Court Correctly Found No Motivation to Arrive at the Individual Elements of the Claimed Dosing Regimens

Because "[t]he determination of obviousness is made with respect to the subject matter ***as a whole***, not separate pieces of the claim," *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed. Cir. 2008), the district court's finding that Teva failed to present credible evidence of a motivation to modify the 548 Protocol is dispositive of nonobviousness. The district court's findings regarding the individual elements of the claims were also correct.

a. The District Court Correctly Found No Motivation to Use the Deltoid for Loading Doses

Appellants contend that because the deltoid muscle was a known injection site, the district court should not have "placed [any] significance" on injection site in analyzing obviousness. Br. 51. But the trial testimony of skilled scientists did not support this contention. The trial record established that, as of the priority date, paliperidone palmitate, and indeed all other antipsychotic LAIs, were administered in the gluteal muscle, in part because the large injection volumes of LAIs are very painful when injected in the deltoid. Appx74-78; Appx11582(1582:11-18); Appx11898(1898:19-1899:10); Appx11957(1957:16-17);

Appx20104. And although Appellants rely on "routine experimentation" to show obviousness (Br. 49-50), Teva's expert, Dr. Wermeling, expressly disavowed the opinion that "routine optimization" would have led a POSA to the claimed invention. Appx10361-10363(361:25-363:1). The objective evidence confirmed that the development of the claimed inventions was anything but routine. *Supra* at 9-15.

Instead of endorsing Appellants' "routine experimentation" theory, Dr. Wermeling testified that Goodman and Gibaldi would have "motivate[d] a POSA to arrive at the claimed regimens because they teach that deltoid injections lead to faster absorption than gluteal injections." Appx75-77. The court did not err in discrediting this testimony. Dr. Wermeling ignored Goodman's teaching, "persuasively conveyed" by Dr. Sinko, that deltoid injections would ***not*** be expected to lead to faster absorption in the claimed long-acting formulations, because the formulation was believed to control how fast the drug is absorbed, thus rendering the injection site irrelevant. Appx76; Appx11533-11536(1533:23-1536:25); Appx12263(2263:14-22). Similarly, Dr. Wermeling "admitted[ly]" ignored Gibaldi's teaching that depot injections are not suitable for initiating therapy, "selectively rel[ying] on only some of Gibaldi's teachings in forming his opinions rather than the reference as a whole." Appx77.

Finally, the court correctly found that some patients' preference for deltoid injections did "not satisfy Defendant's burden" of showing motivation to use the deltoid site in the claimed invention. Appx77-78. Since no existing antipsychotic LAI used the deltoid and the prior art "suggest[ed] administering depots in the gluteal muscle over the deltoid muscle," Appx78, it was unclear whether this preference applied to antipsychotic LAIs at the time of the invention. Moreover, the alleged "individualized" preferences of some patients for deltoid injections (Appx78) would not have led to the claimed general dosing regimens, which require administration of specific doses into specific injection sites on specific days, along with specific maintenance doses and particle size requirements.

b. The District Court Correctly Found that a POSA Would Not Have Been Motivated to Use Unequal Loading Doses

The district court correctly found that Teva failed to prove the obviousness of the claimed inventions' sequence of two unequal loading doses. Appellants contend that the claimed sequence of loading doses should have been "presumed obvious" because the amounts of the doses were disclosed in the prior art, and because the general concept of loading doses was known. Br. 52-53. But as the district court correctly observed, the "unique combination of elements" in the claimed dosing regimens do not fall within any prior-art range. Appx114; *see*

Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1320 (Fed. Cir. 2004) (no presumption of obviousness "[w]here an invention is contended to be obvious based upon a combination of elements"); *cf. Kaneka Corp. v. Xiamen Kingdomway Grp. Co*., 790 F.3d 1298, 1306 (Fed. Cir. 2015) (where method claim "recite[s] an order" the claim is construed to require a specific sequence of steps). Furthermore, the record did not support a theory of "routine optimization" necessary to establish a presumption of obviousness. Appx10361(361:25-363:1); *supra* at 9-15, 47-48; *infra* at 56.

Instead of "routine optimization," Dr. Wermeling relied on Ereshefsky and Karagianis to argue that unequal loading doses would have been obvious. But as the district court found, these references involved "different drugs and different formulations" than paliperidone palmitate LAI, would not have motivated the specific combinations of the claimed general dosing regimens because they taught individualized dosing rather than a "protocol-dosing regimen," and, in any event, did not disclose unequal doses at all. Appx78-80; Appx10517-10518(517:25-518:6); Appx10525-10526(525:23-526:4); Appx11569-11570(1569:18-1570:9). These findings were based on a careful analysis of the trial testimony and cannot reasonably be described as "disregarding the perspective of a skilled artisan." Br. 48.

c. The District Court Correctly Found that the '544 Patent Taught Away from the Particle Size of Claims 20-21

Appellants contend that the particle-size limitations of claims 20-21 would have been obvious because particle size is a "results-effective variable," which a POSA could have optimized "by routine experimentation." Br. 56. Alleged optimization within a range does not render an invention obvious, however, when "the prior art taught away from the claimed invention." *Allergan, Inc. v. Sandoz Inc*., 796 F.3d 1293, 1305 (Fed. Cir. 2015). The district court correctly found that the '544 patent taught away from the claimed particle size.

Appellants argue that the '544 patent's selection of a different formulation for further investigation is not teaching away. Br. 57-58. But "[w]hat the prior art teaches" and "whether a reference teaches away from the claimed invention are questions of fact." *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1335 (Fed. Cir. 2021) (internal quotation marks omitted). A prior art reference teaches away from the claimed invention "if a skilled artisan upon reading the references, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken in the claim." *Id*. (internal quotation marks omitted). That is exactly what the district court found. The court credited Dr. Sinko's testimony that a POSA would have been dissuaded by the '544 patent's teaching that a formulation with the claimed

particle-size distribution (Formulation B) lacked desirable characteristics and had not been chosen for further investigation. Appx85 & n.30.

AstraZeneca is directly on point. There, the Rogueda reference disclosed several formulations, including two "control formulations" relied upon for appellee's obviousness argument. *AstraZeneca*, 19 F.4th at 1336. Rogueda did not explicitly disparage those formulations, but taught that different formulations had performed better. *Id.* The patentee's expert testified "that a skilled artisan" reading the reference "would not have used the control formulations." *Id.* at 1336-37. The "district court properly relied on expert testimony regarding how a skilled artisan would interpret the data in Rogueda" in finding that Rogueda taught away from the claimed formulation. *Id.* at 1337.

As in *AstraZeneca*, the district court here credited Dr. Sinko's testimony that a POSA would "'eliminate . . . [Formulation] B' from further consideration based on 'the two critical parameters, the particle size and surface area'" and because the '544 patent selected different formulations for further research. Appx85. Appellees have identified no error in the court's reliance on Dr. Sinko's testimony to find teaching away.

C. For the Renal Impairment Claims (Claims 10 and 13), the District Court Properly Rejected Teva's Evidence of Motivation and Did Not Read a Limitation into the Claims

For claims 10 and 13, Appellants argue that the district court read a limitation into the claims when it referred to "mild renal impairment" in its analysis of obviousness. Br. 46-48. That is incorrect. As with the general dosing regimen claims, the court simply considered and correctly rejected the renal-impairment motivation theory that Teva offered at trial. Appx81-83. The district court did not require Teva to prove obviousness of unclaimed elements when it rejected Teva's theory. *See supra* at 26; *Immunex*, 964 F.3d at 1066-67; *Intelligent Bio-Sys.*, 821 F.3d at 1368.

At trial, Teva's position was that a POSA would have been motivated to reduce doses by 50% for patients with "mild renal impairment." When Dr. Wermeling was asked on direct examination to identify a dosing regimen a POSA "would be motivated to use to treat a patient with schizophrenia having renal impairment," he answered:

> We have the oral tablet formulation, in which the prescribing information requires a 50 percent dose reduction from the maximum dose ***for patients with mild renal impairment***. So if you then follow that, it would have been reasonable to do the 50 percent reduction for the loading dose strategy of 75 [mg-eq.] vs. the 150 [mg-eq.].

Appx10332-10333(332:21-333:12). Dr. Wermeling's focus on mild renal impairment was understandable, because both parties' medical experts agreed that

paliperidone palmitate LAI "is not designed to be given to patients with moderate or severe renal impairment." Appx121.

But as the district court correctly found, Dr. Wermeling's theory of motivation was not supported by the references he relied upon. Dr. Wermeling relied on three references concerning oral paliperidone: "Cleton 2007," the "Invega ER Label," and the "591 Application." Only two of these references dealt with renal impairment, and these pointed in different directions, with Cleton 2007 suggesting no reduction for patients with mild renal impairment and the Invega ER Label, according to the "convincing[]" testimony of Dr. Sinko, suggesting a smaller reduction. Appx81-82; Appx11586-11588(1586:11-1588:6). The 591 Application is not directed to renal impairment at all. Appx82.

Furthermore, as the district court pointed out, Teva's obviousness theory for the renal impairment claims relied on the same combination of references it relied on for claim 2 (the 548 Protocol, the '544 patent, WO 384, and a variety of secondary references). Appx81. Indeed, Teva's post-trial briefing began by identifying the "difference between the general dosing regimens of claim 2 and the regimens of claims 10 and 13" and contending that this difference would have been obvious. Appx1437. To the extent Teva's argument started from claim 2, the district court correctly pointed out that a fifty percent reduction would not have led to the loading doses of claims 10 and 13. Appx83. Similarly, a fifty

percent reduction from claim 2 (or from any of the untested regimens in the 548 Protocol) does not result in the dosing regimen of claim 13, with its sequence of two loading doses "of from about 75 mg-eq." and a maintenance dose of 25-50 mg-eq. In any event, because the district court found no credible motivation to modify Teva's primary references to arrive at the "general" dosing-regimen claims with a reasonable expectation of success (*supra* at 22-27), it followed that Teva also failed to prove the obviousness of claims 10 and 13.

D. The District Court Properly Found That the Objective Evidence Supports Nonobviousness

Objective indicia of nonobviousness "may often be the most probative and cogent evidence of nonobviousness," as they serve as "essential safeguards that protect against hindsight bias." *Liqwd, Inc. v. L'Oreal USA, Inc.* 941 F.3d 1133, 1136-37 (Fed. Cir. 2019) (internal quotation marks omitted). The objective evidence is particularly powerful in this case. The district court found that long-felt need, commercial success, praise, unexpected results, skepticism, copying, and the failure of others all provided evidence of nonobviousness. Appx92-116. These factual findings were correct, and they strongly support the conclusion that Teva failed to prove obviousness.

1. Objective Evidence Was Integral to the District Court's Nonobviousness Decision

Appellants contend the district court's findings on objective indicia can be ignored because the court did not specifically say the indicia were "strong" or "independently" sufficient to prove nonobviousness. Br. 58. But the case law imposes no such "magic words" prerequisite to the relevance of objective indicia. To the contrary, objective indicia "must ***always*** be considered before reaching a determination on the issue of obviousness." *Quanergy Sys. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022); *see also Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (objective indicia are "crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements"). Here, the court considered the objective indicia and correctly found that they weigh in favor of nonobviousness.

Furthermore, the district court's findings on objective indicia were integral to its nonobviousness determination. Although Dr. Wermeling did not support the theory, Appx10361-10363(361:25-363:1), Teva contended in post-trial briefing—as Appellants do on appeal—that certain elements of the asserted claims were presumptively obvious because they purportedly involved no more than "routine experimentation" within a prior-art range, Appx114. In addition to correctly rejecting the existence of a presumption (*supra* at 49-51), the district court correctly found that the objective evidence "rebut[ted] any such

presumption." Appx115. *See Galderma Lab'ys, L.P. v. Tolmar, Inc*.,737 F.3d 731, 738 (Fed. Cir. 2013) (alleged presumption of obviousness can be overcome by evidence that "there were new and unexpected results relative to the prior art" or "there are other pertinent secondary considerations"); *Allergan*, 796 F.3d at 1304 (rejecting "presumption of obviousness" argument based on district court's "underlying factual findings" as to objective indicia).

2. The Unchallenged Findings of Skepticism, Long-Felt Need, and Commercial Success Demonstrate the Nonobviousness of the Claimed Inventions

Appellants challenge the district court's findings on unexpected results, copying, industry praise, and blocking patents. Br. 60-74. They do not contest its findings on skepticism at all, and they do not address long-felt need or commercial success except to argue these factors should have been ignored due to supposed blocking patents. The unchallenged findings on these issues strongly support nonobviousness. *E.g.*, *Quanergy*, 24 F.4th at 1415 n.6 ("[A]rguments not raised in the opening brief are waived.").

Skepticism. Outside experts were skeptical of the claimed dosing regimens, telling Janssen that its innovative 150/100 initiation regimen was "risky" and recommending "a lower dose." Appx11074-11075(1074:20-1075:16); Appx20280. The FDA similarly suggesting that Janssen reduce the initiation doses to offer a lower 75 mg-eq. dose. Appx11376(1376:1-16); Appx20375-20377. And

even after FDA approval, psychiatrists remained skeptical of deviating from the established "start low and go slow" wisdom. Appx11108(1108:11-23); Appx11907-11908(1907:7-1908:8); Appx12426(2426:5-12); Appx49984. Such skepticism "support[s] a conclusion of nonobviousness." *Neptune*, 921 F.3d at 1377 (FDA skepticism); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016) ("Doubt or disbelief" of success of invention weighs against obviousness). Appellants do not contest the district court's findings on skepticism. The word does not appear once in their brief.

Long-felt need. Improving patient adherence to treatment has been a challenge since the advent of antipsychotic medication. Appx11887-11891(1887:14-1891:6). LAIs advanced this effort but, prior to Invega Sustenna, had failed to meet the need for effective long-acting treatment that could be initiated without oral supplementation. Appx11905(1905:4-11); Appx11910-11912(1910:7-1912:19); Appx12348-12349(2348:18-2349:12); Appx12410(2410:8-17). Invega Sustenna's fulfillment of this long-felt need is powerful evidence of nonobviousness "because it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP*, 829 F.3d at 1332; *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) (recognizing the unmet need for "safer, less toxic, and more effective"

antipsychotic therapies). Other than through alleged blocking patents, Appellants fail to challenge the district court's findings.

Commercial success. Invega Sustenna's blockbuster commercial success further corroborates the inventiveness of the claimed dosing regimens. Appx12531-12522(2585:24-2586:5). Net sales have exceeded $1 billion annually every year since 2015. Appx12525-12526(2579:11-2580:9); Appx19784-19794; Appx55984. Invega Sustenna's share of the second-generation long-acting antipsychotic market was more than twice that of its nearest competitor by the end of 2019. Appx12529(2583:11-18); Appx56039-56046. Teva's expert, Ivan Hofmann, did not disagree with these facts. Appx12780-12784(2834:6-2838:21).

The evidence on nexus was also undisputed. Not only are Invega Sustenna's rapid and sustained efficacy key benefits "that distinguish [the] product from competition," Invega Sustenna has vastly outperformed the oral form of paliperidone—providing further evidence that Invega Sustenna's ***dosing regimen*** (rather than its active ingredient) has driven its blockbuster sales. Appx12540-12541(2594:5-2595:9); Appx12544-12546(2598:21-2601:3). Mr. Hofmann did not dispute that the patented benefits are "driver[s of] demand for Invega Sustenna." Appx12798-12799(2852:17-2853:10). And Appellants do not dispute this on appeal. Commercial success strongly supports nonobviousness. *See Alcon Research Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1371 (Fed. Cir. 2012).

3. The Alleged "Blocking Patents" Do Not Undermine The Weight of Invega Sustenna's Commercial Success and Long-Felt Need

Appellants argue that the powerful objective evidence of commercial success and long-felt need should be disregarded based on alleged "blocking patents." Br. 69-74. This argument fails.

As the district court correctly found, Teva failed to prove the existence of any "blocking patents" at all. Appx111-112. A blocking patent is a patent that would be infringed by the practice of a later invention. *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). But, at trial, Teva presented no analysis of whether the practice of the '906 patent's claims would infringe the alleged blocking patents. After his disastrous opening testimony (resulting in the "credibility issues" cited by the district court, Appx72-73 n.25), Teva chose not to recall its expert Dr. Wermeling to testify as to his rebuttal report on the subject.[7] Appx12456-12457(2456:23-2457:2); Appx12636-12637(2690:17-2691:16); Appx12753-12754(2807:2-2808:25). The lack of any technical analysis of the alleged blocking patents "considerably weaken[ed]" Mr. Hofmann's testimony. Appx112; Appx12732-12735(2786:20-2789:17); Appx12762-12763(2816:18-2817:18); Appx12764-12765(2818:12-2819:4).

[7] At his deposition, Dr. Wermeling testified that he had not even read most of the supposed "blocking patents" identified by Teva. Appx12756(2810:5-10); Appx1934-1935(177:21-178:13).

At trial, as Appellants do on appeal, Mr. Hofmann simply asserted that a "fortress" of Orange Book patents would deter development, with no meaningful analysis of the specific incentives present in this case. Appx12698(2752:15-24). But an analysis of "blocking patents" is a "fact-specific inquiry." *Acorda*, 903 F.3d at 1338-39; *accord Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 731 (Fed. Cir. 2017). Mr. Hofmann did not analyze the specific facts of this case.

By contrast, Janssen's economic expert, Carla Mulhern, presented a credible fact-specific analysis of the actual incentives present in this marketplace. She testified that the extended development timeline for LAIs, combined with the statutory safe harbor that allows for drug development work prior to the expiration of a patent, provided ample opportunity for competitors to develop paliperidone palmitate dosing regimens notwithstanding any alleged blocking patents. In fact, such safe-harbor development repeatedly occurred in the LAI market. Appx12584(2638:7-20); Appx12572-12573(2626:22-2627:20); Appx12574-12575(2628:7-2629:15); Appx12769-12770(2823:22-2824:22). Indeed, Teva itself began to conduct research on paliperidone palmitate long before the issuance of the '906 patent. Appx12786(2840:8-20); Appx56125-56147; Appx56324-56325; Appx56337-56338(61:21-62:14); Appx56406-56411. After careful consideration of the evidence, the district court found "***[o]n these facts***" that "the alleged

blocking patents did not discourage innovation ***in this case***." Appx114. That finding was correct and certainly not clearly erroneous.

4. The Claimed Dosing Regimens Unexpectedly Achieved Safe, Rapid, and Sustained Treatment for Schizophrenia

Appellants challenge the district court's finding of unexpected results, contending there was no difference "in kind" between the closest prior art and the patented dosing regimen. Br. 61-62. But the 548 Protocol, the closest prior art, had no results at all, so it provided no basis for POSAs to reject the conventional wisdom of "start low and go slow." Appx95. Furthermore, the claimed dosing regimens achieved a difference in kind from the dosing regimens in the 548 Protocol. *See, e.g.*, *Leo Pharm.*, 726 F.3d at 1358 (inventor-submitted test results provided evidence of unexpected results); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1351 (Fed. Cir. 2012) (evidence of unexpected results from inventor testimony). The PSY-3003 trial (corresponding to the 548 Protocol) failed to show ***any*** efficacy for most doses and for U.S. subjects, and failed to show rapid efficacy for any subjects, Appx11061-62(1061:21-1062:11); Appx22786-22792, whereas the claimed regimens showed rapid efficacy for the vast majority of subjects, Appx11098(1098:10-18); Appx39152. That is not simply a difference of degree, it is a difference in kind. Appx11105-11106(1105:10-1106:9); Appx12436(2436:2-17); Appx56123.

Compare Allergan, 796 F.3d at 1306-07 (development of safe and effective medication where expectation was for intolerable side effects is a difference "in kind"), *with Galderma*, 737 F.3d at 739 ("small percentage" increase in efficacy was a difference in "degree").

Meanwhile, Appellants' arguments that Janssen's early clinical trials did not actually fail, or did so only because of Janssen's "idiosyncratic bungling," have no support in the record. Br. 64-66. The evidence is clear that the PSY-3003 trial, and the other two failed Phase III trials, failed because of inadequate efficacy and not because of an error in one of PSY-3003's treatment arms. *See supra* at 9-11. And Appellants' contention that Janssen's early failures resulted from using 1.5-inch rather than 2-inch needles is simply wrong. Br. 65. Janssen used a (maximum) 1.5-inch needle in its later, successful trials, and does so ***to this day*** for Invega Sustenna, belying any suggestion that needle length was the issue. Appx39082; Appx41985; Appx50034. Indeed, if the problems with the prior-art dosing regimens could be solved with 2-inch needles, Teva and Mylan could have entered the market years ago with the prior-art dosing regimens. The fact that they have not done so is powerful objective evidence of nonobviousness.

5. There is a Nexus Between The Praise for Invega Sustenna and the Patented Dosing Regimens

Appellants' challenge to the district court's findings on industry praise also fails. The relevant peer-reviewed publications all focused on improved patient

adherence, which the evidence showed was a benefit of the claimed dosing regimens. Appx11914-11916(1914:21-1916:14); Appx10468-10470(468:13-470:13). The *Psychiatric News* publication touted Invega Sustenna's "better adherence rates," Appx20540-20543, the Einarson article associated patient adherence with limiting costs, Appx20563-20539, and the Emsley publication identified patient adherence as a key measure on which Invega Sustenna excelled, Appx20544-20562, at Appx20554. Such praise for "a product that embodies the patent claims" provides evidence of nonobviousness. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc).

6. Copying

Even in the ANDA context, copying provides evidence of nonobviousness when it is not required by the FDA. *Merck*, 874 F.3d at 731. Here, the district court found that Teva was not required to copy the paliperidone palmitate particle size for Janssen's product, but did so nonetheless. Appx102-03. Appellants challenge this finding by conflating the requirement for ***bioequivalence*** with a requirement to copy particle size. Br. 69. But there is no requirement to copy particle size for bioequivalence. Appx103; Appx11625(1625:1-6). Teva's decision to copy particle size provided objective evidence of nonobviousness of claims 20-21.

III. THE DISTRICT COURT PROPERLY FOUND THAT TEVA FAILED TO PROVE CLAIMS 20-21 INDEFINITE

Finally, the district court properly rejected Teva's argument that claims 20-21 are indefinite because they do not adequately specify how to measure "d50" (median particle size). Appx126-135; *see* Appx162(7:32-38); Appx10620-10622(620:18-622:20).

Appellants rely on *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc*., 789 F.3d 1335 (Fed. Cir. 2015), and *Dow Chemical Co. v. NOVA Chemicals Corp. (Canada)*, 803 F.3d 620 (Fed. Cir. 2015), to argue that a claim "is indefinite when it recites a measured property" but "does not convey with reasonable certainty how to measure that property." Br. 75-76. But as the district court correctly noted, differing methods of measuring "must lead to ***meaningfully different results*** in order to render [claims] indefinite." Appx131-132. For this point, the district court relied on *PPG Industries, Inc. v. Guardian Industries Corp*., 75 F.3d 1558, 1562-63 (Fed. Cir. 1996), *Takeda*, 743 F.3d at 1366-67, *Ethicon Endo-Surgery, Inc. v. Covidien, Inc*., 796 F.3d 1312, 1319-22 (Fed. Cir. 2015), and *Ball Metal Beverage Container Corp. v. Crown Packaging Technology, Inc.*, 838 F. App'x 538, 542 (Fed. Cir. 2020), all of which rejected indefiniteness challenges where the claims did not specify the method of measurement, but the challenger failed to show that different measurement methods led to significantly different results.

Despite their one-sided presentation of the law (Appellants fail to cite the principal cases relied on by the district court), Appellants do not contend that the court committed legal error. Instead, they argue that the court erred in finding that Teva failed to prove that the differences between different measurement techniques were significant. The district court's findings are correct.

First, Appellants contend that because different methods of measuring particle size can lead to different results, claims 20-21 must be indefinite. Br. 76-81. This argument is foreclosed by *Takeda*, which Appellants remarkably fail to cite. *Takeda* is directly on point, involving an indefiniteness challenge to the term "average particle diameter"—a virtual synonym of "d50." *Takeda*, 743 F.3d at 1362. In *Takeda*, as here, the parties' experts agreed that particle size can be measured by different methods and that these methods "***can*** produce different results." *Id.* at 1366. Indeed, Teva's expert relied on a verbatim quotation also found in *Takeda*. *Compare* Appx10601(601:6-10), Appx10604(604:4-8), *with Takeda*, 743 F.3d at 1367. But the holding of *Takeda* was that "the mere possibility of different results from different measurement techniques" does not render a claim indefinite. *Id.* at 1366-67. This defeats Appellants' argument.

Appellants further contend that different methods of measuring particle size led to materially different results in the context of the '906 patent. Br. 78-81. But the district court considered the record evidence and correctly found

that it did not establish indefiniteness. Appx134-35. As the district court found, the trial record demonstrated that "different methods of measuring and expressing d50 were likely to produce substantially similar values." Appx134; Appx12195-12196(2195:19-2196:10). Indeed, Teva itself analyzed particle size using multiple methods, found that the results were test results with each other, and had "no issues" ascertaining particle size. Appx134; Appx10651-10652(651:17-652:7); Appx56382-56383(80:9-81:7).

Appellants' contention that Janssen "submitted two different particle-size specifications to the FDA," Br. 79, was contradicted by the testimony of their own expert, who admitted that Janssen only has "one d50 acceptance criteria," Appx10658(658:2-17); Appx54684. As the district court correctly found, Janssen's material scientists resolved an apparent discrepancy between two measurement devices (Coulter and Mastersizer), finding that the discrepancy was due to an "equipment defect" of the Coulter device rather than any inherent uncertainty in the particle size of Janssen's formulation. Appx132 n.52; Appx10660-10662(660:20-662:17); Appx11556-11558(1556:10-1558:9); Appx20633-20635.

Janssen's scientists (acting years before this litigation commenced) prepared an extensive report in which they measured particle size using multiple "orthogonal" (uncorrelated) measurement techniques and found that "three

different methods" "came up with, in essence, the same particle size distribution," demonstrating that the Coulter result was an instrumental "artifact" and that particle size could be measured with reasonable certainty despite the existence of multiple measurement methods. *Id.* Appellants devote multiple pages of their brief to the Mastersizer/Coulter issue, Br. 77-80, yet have nothing to say about this fact other than to baselessly assert it is "unsupported," Br. 80. The district court did not clearly err in finding that Teva had failed to prove indefiniteness.[8]

CONCLUSION

This Court should affirm the district court's judgment.

[8] Appellants also point out that Teva and Janssen, ***using the exact same instrument***, measured different particle sizes for different samples from the same lot of Invega Sustenna. Br. 79. But as Dr. Sinko credibly testified at trial, that does not mean that d50 is indefinite; it simply means that the two samples, although originating from the same lot, had different particle sizes. Appx11559-11560(1559:22-1560:14).

Dated: September 6, 2022

Respectfully submitted,

/s/ Barbara L. Mullin

Barbara L. Mullin
Aron Fischer
Andrew D. Cohen
A. Robert Quirk
Meghan R. Larywon
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, NY 10036
(212) 336-2000
bmullin@pbwt.com

Attorneys for Plaintiffs-Appellants Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica, NV

CERTIFICATE OF SERVICE

I certify that, on September 6, 2022, the non-confidential version of this brief was electronically filed with the Clerk of Court using the CM/ECF system and thereby served on all parties, and the confidential version was served on the following counsel at the email addresses below, under the parties' agreement to accept electronic service of confidential materials.

John C. Quinn, principal counsel for Teva (john.oquinn@kirkland.com)
William H Burgess (william.burgess@kirkland.com)
Jeanna Wacker (jeanna.wacker@kirkland.com)
Christopher Jagoe (christopher.jagoe@kirkland.com)
Justin Bova (justin.bova@kirkland.com)

Deepro R. Mukerjee, principal counsel for Mylan
(deepro.mukerjee@katten.com)
Lance A. Soderstrom (lance.soderstrom@katten.com)
Jitendra Malik (jitty.malik@katten.com)
Eric Werlinger (eric.werlinger@katten.com)
Jillian Schurr (jillian.schurr@katten.com)

/s/ Barbara L. Mullin
Barbara L. Mullin

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Fed. Cir. R. 32(b). This brief contains 13,929 words, excluding the parts of the brief exempted by Fed. Cir. R. 32(b)(2) and Fed. R. App. P. 32(f).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word in a 14-point Times New Roman font.

Dated: September 6, 2022

/s/ Barbara L. Mullin
Barbara L. Mullin